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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

	Application No.	Applicant(s)
Office Action Summary	10/071,136	EDWARDS, DAVID N.
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _24 January 2005_.

2a)☒ This action is **FINAL**.   2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _1-8,10-13 and 23-32_ is/are pending in the application.

    4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _1-8,10-13 and 23-32_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

    a)☐ All   b)☐ Some * c)☐ None of:

      1.☐ Certified copies of the priority documents have been received.

      2.☐ Certified copies of the priority documents have been received in Application No. _____.

      3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

    * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _1/2005_.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

1.   Currently, claims 1-8, 11-13, and newly added claims 23-32 are pending in the instant

application and under examination. All the amendments and arguments have been thoroughly

reviewed but are deemed insufficient to place this application in condition for allowance. The

following rejections are newly applied, as necessitated by amendment. They constitute the

complete set being presently applied to the instant Application. Response to arguments are

included, where applicable. This action is FINAL.

2.   The text of those sections of Title 35, U.S. Code not included in this action can be found

in a prior Office action.

3.   The rejection of claims 1 and 9 under 35 USC 112, first paragraph, made at section 4 of

the previous office action is withdrawn in view of the cancellation of claim 9.

4.   The rejection of claims 1-3 under 35 USC 102(b) made at section 7 of the previous office

action is moot in view of the amendments to claim 1: I) to recite "a sequence which encodes a

transcriptional termination sequence placed immediately 3' to the DNA sequence encoding at

least one GAL4 common peptide" as Fields does not specifically teach a vector where a

transcriptional termination sequence is located immediately 3' to (that is immediately adjacent

to, on the 3' side) the DNA sequence encoding at least one common peptide, and II) to recite a

library having a plurality of vectors, wherein a plurality of cDNA molecules are enriched for 5'

cDNA. The 102(b) rejection has not been applied to the newly added claims as they include the

recitations directed to I) above.

New Grounds of Objection and Rejection

Claim Objections

5.   Claims 4 and 28 are objected to under 37 CFR 1.75(c), as being of improper dependent

form for failing to further limit the subject matter of a previous claim. The limitations of claims

4 and 28 are found in the respective independent claim from which each depends. Additionally,

the independent claims recite a "GAL4 common peptide" whereas the dependent claims 4 and 28

recite [any] common peptide and are actually broader than the claims from which they depend.

Accordingly, the dependent claims 4 and 28 do not further limit the independent claims.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper

dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

6.   Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the

written description requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a New Matter Rejection.

Newly added claim 32 recites "a cDNA molecule having a 5' untranslated region, a

translation initiation codon, and a sequence encoding a protein operable to bind another protein

in a yeast two hybrid assay, the cDNA molecule inserted in the multiple cloning site". The

recitation of "a sequence encoding a protein operable to bind another protein in a yeast two

hybrid assay" is not supported in the specification. At page 11, para 21, last sentence, the

specification teaches "Activation is indicative that the polypeptide encoding by the particular

cDNA insert in a given cell is capable of interaction with the bait polypeptide". The

specification does not teach that "interaction" is limited to "operable to bind to", and therefore

such recitation adds new matter to the claims which is not supported by the specification as

originally filed. This rejection can be overcome by reciting instead 'a sequence encoding a

protein which interacts with another protein in a yeast two hybrid assay".

Indefinite

7.   The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the
> subject matter which the applicant regards as his invention.

8.   Claims 25 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite

for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention.

Claims 25 and 32 recite "the plurality of plasmid vectors" which lacks antecedent basis.

The claims only recite "a plasmid vector" (singular). The claims do not previously recite a

plurality of plasmid vectors, therefore it is not clear what "plurality of plasmid vectors" are being

referred to.

Claim 32 recites the phrase "operable to bind another protein" which is indefinite because

it is not clear if the recitation refers to a protein which binds to another protein, or one that is

capable of binding to another protein but does not necessarily.

Claim Rejections - 35 USC § 102

9.   Claims 1-4, 10, 11, 13, and 23-32 are rejected under 35 U.S.C. 102(a) and 102(e) as

being anticipated by Thukral, S.K. (US Patent 6,103,472, 102(a): August 15, 2000, 102(e) date:

2/20/1998).

Thukral teaches a method of constructing a cDNA library and inserting the library into a

signal trap vector to generate a signal trap library (hybrid gene library having a plurality of

plasmid vectors of instant claim 1, see col. 2, lines 40-50). The signal trap library (hybrid gene

library) taught by Thukral is constructed with vectors such that DNA sequences which control

expression of selection or marker genes, cDNA inserts, and reporter genes are operably linked to

said cDNA and genes and that the signal sequences are inserted in frame to the reporter

polypeptide coding sequences (see col. 7, lines 5-15). Thukral teaches that the vector is pYYa-

41L which is an E. coli –yeast shuttle vector that contains a Bla1 gene for ampicillin resistance

and TRP1 gene for propagation in yeast ('selectable marker sequence' with regard to instant

claim 1, and instant claim 11, see col. 7, lines 15-19). Thukral teaches that the vector contains

ColE1-ORI replication origin for maintenance and propagation in E coli (instant claims 2, 26),

and a 2u origin for replication and propagation in yeast (instant claims 3, 10, 27 and 29, see col.

7, lines 15-19). With regard to instant claims 1, 25 and 32, Thukral also teaches that the vector

contains in order 5' to 3' an ADH promoter (regulatable DNA sequence), a polylinker containing

unique XhI and Not I sites to facilitate directional cloning of random primed cDNAs (multiple

cloning site that does not encode a translational termination sequence and placed immediately 3'

to the regulatable DNA sequence, see also col. 10, lines 34-37), a leaderless a-amylase gene

encoding amino acids 29-624 of a-amylase (a DNA sequence encoding at least one common

peptide and not containing a translation initiation codon which is place 3' to the multiple cloning

site) (see col. 7, lines 20-26), or amino acids 82-624 (see col. 10, lines 58-67). See also example

3 for construction of hybrid gene cDNA library. Although Thukral does not explicitly state that

the multiple cloning site does not contain a translational termination sequence, such is an

inherent teaching of Thukral because the hybrid protein that is constructed, as taught by Thukral,

contains the protein encoded by the random primed cDNA on the N-terminal side fused to the

leaderless a-amylase protein (common peptide) on the C-terminal side. With regard to instant

claims 1, 4, 25, 28, and 32, Thukral teaches that after the a-amylase sequence, the vector contains

an ADH terminator sequence (see col. 7, lines 23 and 24). With regard to the limitation reciting

"wherein the hybrid protein region lacks a translation initiation codon 5' of the cDNA, although

Thukral does not explicitly teach that the vector lacks a translation initiation sequence other than

that in a cDNA insert, Thukral does teach at col 10, lines 34-40, how the vectors pYYA-41L and

pYYA-2 were made. Thukral teaches that in making the vectors from pGBT9, sequences

between the ADH promoter and ADH terminator were removed. Thus, the sequence directed to

the GAL4 translation initiation sequence was specifically taught by Thukral to have been

removed. The vectors are then described by what elements they do contain at col 7. Thukral

teaches that the cDNA molecules can be selected for the presence of 5' ends (see col. 4, lines 19-

25; instant claimed limitation "wherein the plurality of plasmid vectors contain a plurality of

cDNA molecules generated using random primers and enriched for 5' cDNA..."). With regard

to the limitations reciting "at least one GAL4 common peptide", or "or portions of the GAL4

yeast transcriptional activator" or "or portions of the GAL4 DNA binding domain" such term is

not specifically defined in the specification to be limited to any particular portion of GAL 4. A

"portion of GAL4" or a "GAL4 common peptide" encompasses a minimum of 2 consecutive

amino acids from any portion of GAL4. The portion of a-amylase taught by Thukral inherently

possesses at least 2 consecutive amino acids from any portion of GAL4, including the yeast

activation domain and the DNA binding domain. For example, a-amylase contains 2 consecutive

serine residues which can be found in both the DNA binding domain as well as the activation

domain of GAL4. With regard to the broad recitation "wherein at least one of the plurality of

plasmid vectors is operable in a GAL4 yeast two hybrid assay" the claimed vectors have not

been specifically defined in the specification to be limited to any type of activity or operability,

nor does the claim limit the vectors to any specific type of "operability". Thus the broad

recitation imparts no structural limitation on the claimed vectors other than, for example, that

they be able to be cloned in a cell also used for a yeast two hybrid assay, which does not

distinguish the instant claims from the disclosure of Thukral. Furthermore, it should be noted

that the claims are directed to products, not methods directed to a yeast two hybrid assay with

specific steps. As such, the claimed recitation is drawn to an intended use limitation that is not

given patentable weight because it provides no specific structural limitation to distinguish the

claimed products from those disclosed by Thukral.

Response to Arguments

10.   The response traverses the rejection. The response asserts that Thukral does not relate to

assays such as yeast two hybrid assays and that Thukral's stated goal discloses use of the

common peptide reporter sequences that "confer a property or activity when secreted which may

be readily assayed" and thus does not relate to assays such as yeast two hybrid assays. This

argument has been thoroughly reviewed but was found unpersuasive. The broad recitation

"wherein at least one of the plurality of plasmid vectors is operable in a GAL4 yeast two hybrid

assay" the claimed vectors have not been specifically defined in the specification to be limited to

any type of activity or operability, nor does the claim limit the vectors to any specific type of

"operability". Thus the broad recitation imparts no structural limitation on the claimed vectors

other than, for example, that they be able to be cloned in a cell also used for a yeast two hybrid

assay, which does not distinguish the instant claims from the disclosure of Thukral.

Furthermore, it should be noted that the claims are directed to products, not methods directed to a

yeast two hybrid assay with specific steps. As such, the claimed recitation is drawn to an

intended use limitation that is not given patentable weight because it provides no specific

structural limitation to distinguish the claimed products from those disclosed by Thukral. The

response further traverses that it is not clear whether or not the plasmids of Thukral contain an

independent start sequence or rely upon the translational start sequence in the encoded protein.

The response asserts that the plasmids used by Thukral appear to have been derived by

Clonetech's pGBT9 plasmid, which contains the GAL4 translation initiation sequence before it's

multiple cloning site and that it does not appear to have been removed during the creation of

YYA-41L or pYYA-2. This argument has been thoroughly reviewed but was found

unpersuasive. Thukral teaches that in making the vectors from pGBT9, sequences between the

ADH promoter and ADH terminator were removed (see col. 10, lines 33-35). Thus, the

sequence directed to the GAL4 translation initiation sequence, which lies between the ADH

promoter and ADH terminator as shown in the map for pGBT9 provided in the response, was

specifically taught by Thukral to have been removed. The response's arguments as to why

Thukral might have wanted to keep the pGBT9 translation initiation sequence is thus also not

persuasive. At page 10, the response asserts that Thukral does not disclose a cDNA population

generated using random primers and hence enriched in it's representation of 5' region of genes.

This argument has been thoroughly reviewed but was not found persuasive. The claims are

drawn to products, not to methods of making a library. The only weight that can be given to a

recitation of how the cDNAs were obtained is wherein the recitation imparts a structural

limitation on the claimed products. In this case, the cDNAs in the library are enriched for 5'

cDNA, which is taught by Thukral. Thukral specifically teaches that cDNAs could be selected

for 5' ends (col. 4, lines 24-25). Therefore, the claimed recitation does not structurally

distinguish the claimed products over those disclosed by Thukral. Arguments with regard to

claims 25 and 32 are not persuasive for the reasons made of record above. Additionally, it

should be noted that claims 25 and 32 are drawn to a single vector, and not to multiple vectors,

therefore arguments to a cDNA population are additionally not persuasive as the vector is only

directed to include "a cDNA molecule", not a population.

Claim Rejections - 35 USC § 103

11.   Claims 25-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fields in

view of Thukral.

Fields teaches a kit for making, as well as vector libraries which include a 'second vector'

which contains a 'second chimeric gene' (see col. 5, lines 40-45). Fields teaches that the vectors

can be used in yeast two hybrid assays to detect if a multiplicity of proteins, such as those

encoded by the entire genome, can be simultaneously tested for interaction with a known protein

(see col. 3, lines 1-5). Fields teaches that the vector in the library contains a promoter, a

transcription termination signal and a chimeric gene that includes a DNA sequence that encodes

a transcriptional activation domain and a unique restriction site(s) to insert a DNA sequence

encoding a test protein or protein fragment into the vector such that a second hybrid protein is

formed (see col. 5, lines 45-50) which is composed of the test protein fused to the transcriptional

activation domain. Fields teaches that the activation domain can be that of GAL4 and teaches

that the second hybrid protein may be encoded on a library of plasmids that contain genomic,

cDNA , or synthetically generated DNA sequences fused to the DNA sequence encoding the

transcriptional activation domain. Fields specifically exemplifies vectors which contains the

SNF4 promoter (regulatable DNA sequence) and SNF4 gene lacking the last amino acid of SNF4

(see col. 9, lines 12-15; and col. 11, lines 2-5) fused to the GAL4 activation domain (amino acids

768-881) to form an SNF4-GAL4 fusion protein. Fields teaches a vector which contains a single

cDNA molecule which is 5' of the common peptide encoding sequence (GAL4), wherein the

common peptide does not contain a translation initiation codon. Additionally, the vectors of the

library of Fields could not have a translational termination sequence at the multiple cloning site

because the common peptide GAL4, would not be fused to the C terminal end of the SNF4 gene

after translation, should one exist. Additionally, the recitation of "wherein the plurality of

plasmid vectors contain a plurality of cDNA molecules generated using random primers and

enriched for 5' cDNA from represented genes..." imparts no structural limitation on the claimed

vector because the claims are drawn to only one vector, and not to a plurality of plasmid vectors.

The cDNA molecule inserted in the vector could have been generated using random primers,

therefore the element meets the claimed limitation. Fields specifically teaches that the 'second

vector' further includes a means for replicating itself in the host cell, which Fields specifically

teaches encompasses yeast cells (see col. 4, lines 21-22), and in bacteria (see col. 5-6, bridging

para). Fields also teaches that the 'second vector' contains a marker gene that permits selection

of cells containing the marker gene from cells which do not contain it. Although Fields teaches

that the vectors include a transcriptional termination sequence, Fields does not specifically teach

one that is placed immediately 3' to the DNA sequence encoding at least one common peptide

(claims 25, 28, and 32). Fields also does not specifically teach a yeast origin of replication that is derived from the natural 2 micron yeast plasmid (claim 29).

However, Thukral teaches and exemplifies a method of constructing a hybrid gene cDNA library. The vectors in the library exemplified by Thukral contain, 5' to 3', a promoter (yeast ADH 1 promoter), a polylinker containing restriction sites for directional cloning of random primed cDNAs, a common peptide, and a transcriptional terminator sequence immediately 3' to the sequence encoding the common peptide (col. 10, lines 34-37; col. 7, lines 20-26; col. 10, lines 58-67). See also example 3 for construction of hybrid gene cDNA library. Although Thukral does not explicitly state that the multiple cloning site does not contain a translational termination sequence, such is a property of the teaching of Thukral because the hybrid protein that is constructed, as taught by Thukral, contains the protein encoded by the random primed cDNA on the N-terminal side fused to the leaderless a-amylase protein (common peptide) on the C-terminal side.

With regard to instant claims 25, 28, and 32, Thukral teaches that after the a-amylase sequence, the vector contains an ADH terminator sequence (see col. 7, lines 23 and 24). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct a vector for hybrid gene libraries as taught by Fields and to include a transcriptional terminator sequence immediately 3' to the common peptide to achieve the expected advantage of producing a hybrid protein with a test protein on the amino terminal end of the protein and the common peptide on the C terminal end, as taught by both Fields and Thukral. For a hybrid protein to be produced as taught by both Fields and Thukral, a transcriptional terminator sequence would need to be present to ensure that the common peptide is on the C terminal end of the hybrid protein. The ordinary artisan would have been motivated

to include a transcriptional terminator sequence immediately 3' to the sequence encoding the

common peptide to achieve a hybrid protein as taught by both Fields and Thukral. Additionally,

Thukral specifically teaches to construct a transcriptional terminator sequence immediately 3' to

the sequence encoding the common peptide to construct a hybrid protein as taught by Thukral.

With regard to instant claims 26, 27, and 29, Thukral teaches that the vector contains

ColE1-ORI replication origin for maintenance and propagation in E coli and a 2u origin for

replication and propagation in yeast (see col. 7, lines 15-19). Therefore, it would have been

prima facie obvious to one of ordinary skill in the art at the time the invention was made to

construct a vector for hybrid gene libraries as taught by Fields and to include origin of replication

for both E. coli and yeast, as specifically taught by Thukral to achieve the expected advantage of

constructing a vector which allows for propagation of vectors in either a bacteria or yeast host

cell as taught by Fields. The ordinary artisan would have been motivated to include the origin of

replication for yeast as taught by Thukral because Fields teaches that vectors should be

replicatable in either bacteria or yeast and Thukral teaches origin of replication for yeast include

that derived from the natural 2-micron yeast plasmid. As Fields teaches that the vectors should

be capable of propagation in different host cells including yeast and bacteria, the ordinary artisan

would have been further motivated to include origins of replication for yeast and bacteria in the

same vector, as taught and exemplified by Thukral, for the purpose of constructing a more

versatile vector that would allow for propagation in different types of host cells, such as yeast

and bacteria. The ordinary artisan would have had a reasonable expectation of success that a

vector could be constructed in this way, because Thukral teaches the successful construction of

vectors that contain origins of replication for both yeast and bacteria.

With regard to claim 31, although Fields does not specifically construct a vector wherein the common peptide on the C terminal end of the fusion protein is the GAL4 DNA binding domain, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to also construct vectors wherein the common peptide on the C terminal end of the fusion protein is the GAL4 DNA binding domain in order to make a number of different vectors that could be used in the yeast two hybrid assays taught by Fields. The ordinary artisan would have been motivated to construct a vector wherein the common peptide on the C terminal end of the fusion protein is the GAL4 DNA binding domain for use in the method of Fields for the purpose of providing a versatile number of different constructs that could by used to practice the method of Fields. The ordinary artisan would have had a reasonable expectation of success that GAL4 common peptides including the GAL4 DNA binding domain, could be placed at the C terminal end of the fusion protein because Fields teaches successful yeast two hybrid assays wherein a GAL4 common peptide (yeast transcriptional activator) is on the C terminal end of the fusion protein.

Response to Arguments

12.   The response traverses the rejection of claims held to be unpatentable over Fields in view of Thukral. The response asserts that one skilled in the art would not combine Thukral and Fields because the construct of Thukral relates to secreted proteins which would seriously hamper, if not prevent the function of proteins in a two hybrid assay, which is an assay taught by Fields. This argument has been thoroughly reviewed but was not found persuasive. While Fields and Thukral construct vector libraries for different purposes, the vectors taught by both patents have common elements which are important to vector libraries in general and not specific to signal trap vectors. Additionally, these elements are placed in similar orientations with respect

to each other: for example, the MCS, the common peptide, etc. The specific placement of the transcription termination site in the Thukral patent (3' to the common peptide verses immediately adjacent on the 3' side of the common peptide) does not appear to be placed there for any reason relating to the construct being a signal trap vector. It would have been obvious to the ordinary artisan at the time the invention was made that placing the transcription terminator sequence immediately 3' to the sequence encoding the common peptide would ensure that the encoded common peptide was on the C terminal end of the fusion protein. For a hybrid protein (where the common peptide was on the C terminal end of the fusion protein) to be produced as taught by Fields and as taught by Thukral, a transcriptional terminator sequence would need to be present to ensure that the common peptide is on the C terminal end of the hybrid protein. The ordinary artisan would have been motivated to include a transcriptional terminator sequence immediately 3' to the sequence encoding the common peptide to achieve a hybrid protein as taught by both Fields and Thukral. Additionally, Thukral specifically teaches to construct a transcriptional terminator sequence immediately 3' to the sequence encoding the common peptide to construct a hybrid protein.

The response additionally asserts that both the disclosure of Fields and that of Thukral lack any teaching or suggestion to use a cDNA population enhanced for 5' ends. This argument has been thoroughly reviewed but was found unpersuasive. The recitation of "wherein the plurality of plasmid vectors contain a plurality of cDNA molecules generated using random primers and enriched for 5' cDNA from represented genes..." imparts no structural limitation on the claimed vector because the claims are drawn to only one vector, and not to a plurality of plasmid vectors. The cDNA molecule inserted in the vector could have been generated using random primers, therefore the element meets the claimed limitation.

13.   Claims 1-4, 10-13, and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable

over Fields in view of Thukral, further in view of Guegler (Guegler et al; US Patent 6,083,727).

Fields teaches a kit for making, as well as vector libraries which include a 'second vector'

which contains a 'second chimeric gene' (see col. 5, lines 40-45). Fields teaches that the vector

in the library contains a promoter, a transcription termination signal and a chimeric gene that

includes a DNA sequence that encodes a transcriptional activation domain and a unique

restriction site(s) to insert a DNA sequence encoding a test protein or protein fragment into the

vector such that a second hybrid protein is formed (see col. 5, lines 45-50) which is composed of

the test protein fused to the transcriptional activation domain. Fields teaches that the activation

domain can be that of GAL4 and teaches that the second hybrid protein may be encoded on a

library of plasmids that contain genomic, cDNA , or synthetically generated DNA sequences

fused to the DNA sequence encoding the transcriptional activation domain. Fields specifically

exemplifies vectors which contains the SNF4 promoter (regulatable DNA sequence) and SNF4

gene lacking the last amino acid of SNF4 (see col. 9, lines 12-15; and col. 11, lines 2-5) fused to

the GAL4 activation domain (amino acids 768-881) to form an SNF4-GAL4 fusion protein.

Fields teaches a vector which contains a single cDNA molecule which is 5' of the common

peptide encoding sequence (GAL4), wherein the common peptide does not contain a translation

initiation codon. Additionally, the vectors of the library of Fields could not have a translational

termination sequence at the multiple cloning site because the common peptide GAL4, would not

be fused to the C terminal end of the SNF4 gene after translation, should one exist. Fields

specifically teaches that the 'second vector' further includes a means for replicating itself in the

host cell, which Fields specifically teaches encompasses yeast cells (see col. 4, lines 21-22), and

in bacteria (see col. 5-6, bridging para). Fields also teaches that the 'second vector' contains a

marker gene that permits selection of cells containing the marker gene from cells which do not

contain it. Fields teaches that the vectors can be used in yeast two hybrid assays to detect if a

multiplicity of proteins, such as those encoded by the entire genome, can be simultaneously

tested for interaction with a known protein (see col. 3, lines 1-5). Although Fields teaches that

the vectors include a transcriptional termination sequence, Fields does not specifically teach one

that is placed immediately 3' to the DNA sequence encoding at least one common peptide

(claims 1 and 4), which is the ADH1 termination sequence (claim 13). Fields also does not

specifically teach the yeast origin of replication that is derived from the natural 2 micron yeast

plasmid (claim 10). Additionally, Fields does not teach selectable marker sequences: bacterial

ampicillin gene and TRP 1 nutritional auxotrophy gene (claim 11) or bacterial kanamycin

resistance gene and yeast URA3 nutritional auxotrophy gene.

However, Thukral teaches and exemplifies a method of constructing a hybrid gene cDNA

library. The vectors in the library exemplified by Thukral contain, 5' to 3', a promoter (yeast

ADH 1 promoter), a polylinker containing restriction sites for directional cloning of random

primed cDNAs, a common peptide, and a transcriptional terminator sequence immediately 3' to

the sequence encoding the common peptide (col. 10, lines 34-37; col. 7, lines 20-26; col. 10,

lines 58-67). See also example 3 for construction of hybrid gene cDNA library. Although

Thukral does not explicitly state that the multiple cloning site does not contain a translational

termination sequence, such is a property of the teaching of Thukral because the hybrid protein

that is constructed, as taught by Thukral, contains the protein encoded by the random primed

cDNA on the N-terminal side fused to the leaderless a-amylase protein (common peptide) on the

C-terminal side.

With regard to instant claims 1, 4, and 13, Thukral teaches that after the a-amylase sequence, the vector contains an ADH terminator sequence (see col. 7, lines 23 and 24). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct vectors for hybrid gene libraries as taught by Fields and to include a transcriptional terminator sequence immediately 3' to the common peptide to achieve the expected advantage of producing a hybrid protein with a test protein on the amino terminal end of the protein and the common peptide on the C terminal end, as taught by both Fields and Thukral. For a hybrid protein to be produced as taught by both Fields and Thukral, a transcriptional terminator sequence would need to be present to ensure that the common peptide is on the C terminal end of the hybrid protein. The ordinary artisan would have been motivated to include a transcriptional terminator sequence immediately 3' to the sequence encoding the common peptide to achieve a hybrid protein as taught by both Fields and Thukral. Additionally, Thukral specifically teaches to construct a transcriptional terminator sequence immediately 3' to the sequence encoding the common peptide to construct a hybrid protein as taught by Thukral. The ordinary artisan would have been further motivated to include the transcriptional terminator sequence of ADH1 because Thukral teaches that such successfully functions in constructing hybrid gene libraries that produce hybrid proteins as taught by both Fields and Thukral.

With regard to instant claims 11 and 12, Thukral teaches that the vector should contain marker genes such as a gene for ampicillin resistance, or a gene for bacterial kanamycin resistance for growth in bacterial, and TRP1 gene or URA gene for propagation in yeast (see col. 7, lines 15-19; col. 4 line 67; col. 5, lines 4-5). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct a vector for hybrid gene libraries as taught by Fields and to include specific selection markers as taught

by Thukral to achieve the expected advantage of constructing a vector which allows for selection

of cells containing the marker gene from cells which do not contain it, as taught by Fields. The

ordinary artisan would have been motivated to include the marker genes as taught by Thukral

because Fields teaches that vectors should contain a marker and Thukral teaches that marker

genes include those for ampicillin or kanamycin resistance in bacteria and URA or TRP1 for

propagation in yeast. As Fields teaches that the vectors should be capable of propagation in

different host cells including yeast and bacteria, the ordinary artisan would have been further

motivated to include selectable markers for propagation in yeast and bacteria in the same vector,

as taught and exemplified by Thukral, for the purpose of constructing a more versatile vector that

would allow for propagation in different types of host cells, such as yeast and bacteria. The

ordinary artisan would have had a reasonable expectation of success that a vector could be

constructed in this way, because Thukral teaches the successful construction of vectors that

contain selectable markers for both bacteria and yeast, in the same vector.

With regard to instant claims 2, 3, and 10, Thukral teaches that the vector contains

ColE1-ORI replication origin for maintenance and propagation in E coli and a 2u origin for

replication and propagation in yeast (see col. 7, lines 15-19). Therefore, it would have been

prima facie obvious to one of ordinary skill in the art at the time the invention was made to

construct a vector for hybrid gene libraries as taught by Fields and to include origin of replication

for both E. coli and yeast, as specifically taught by Thukral to achieve the expected advantage of

constructing a vector which allows for propagation of vectors in either a bacteria or yeast host

cell as taught by Fields. The ordinary artisan would have been motivated to include the origin of

replication for yeast as taught by Thukral because Fields teaches that vectors should be

replicatable in either bacteria or yeast and Thukral teaches origin of replication for yeast include

that derived from the natural 2-micron yeast plasmid. As Fields teaches that the vectors should

be capable of propagation in different host cells including yeast and bacteria, the ordinary artisan

would have been further motivated to include origins of replication for yeast and bacteria in the

same vector, as taught and exemplified by Thukral, for the purpose of constructing a more

versatile vector that would allow for propagation in different types of host cells, such as yeast

and bacteria. The ordinary artisan would have had a reasonable expectation of success that a

vector could be constructed in this way, because Thukral teaches the successful construction of

vectors that contain origins of replication for both yeast and bacteria.

With regard to claim 24, although Fields does not specifically construct a vector wherein

the common peptide on the C terminal end of the fusion protein is the GAL4 DNA binding

domain, it would have been prima facie obvious to one of ordinary skill in the art at the time the

invention was made to also construct vectors wherein the common peptide on the C terminal end

of the fusion protein is the GAL4 DNA binding domain in order to make a number of different

vectors that could be used in the yeast two hybrid assays taught by Fields. The ordinary artisan

would have been motivated to construct a vector wherein the common peptide on the C terminal

end of the fusion protein is the GAL4 DNA binding domain for use in the method of Fields for

the purpose of providing a versatile number of different constructs that could by used to practice

the method of Fields. The ordinary artisan would have had a reasonable expectation of success

that GAL4 common peptides including the GAL4 DNA binding domain, could be placed at the

C terminal end of the fusion protein because Fields teaches successful yeast two hybrid assays

wherein a GAL4 common peptide (yeast transcriptional activator) is on the C terminal end of the

fusion protein.

Fields in view of Thukral do not teach a hybrid gene library comprising a plurality of

plasmid vectors wherein the plurality of plasmid vectors contain a plurality of cDNA molecules

generated using random primers and enriched for 5' cDNA from represented genes. However,

Guegler teaches that a problem with cDNA libraries is that they have a significant proportion of

incomplete cDNAs and a significant underrepresentation of sequences close to the 5' end of

mRNAs (see col. 1, lines 30-50). Guegler teaches that a way to improve traditional cDNA

libraries is to use cDNA that has the 5' information, which can be generated using random

primers and results in a 5' enriched cDNA library (see para bridging cols 1-2). Therefore, it

would have been prima facie obvious to one of ordinary skill in the art at the time the invention

was made to improve the hybrid gene library having a plurality of plasmid vectors of Fields in

view of Thukral, to include cDNAs in the library which are enriched for 5' cDNA from

represented genes as taught by Guegler to ensure that the proteins being tested for interaction

with a known protein in the yeast two hybrid method of Fields encode full length proteins. The

ordinary artisan would have been motivated to construct a hybrid gene library having a plurality

of plasmid vectors of Fields in view of Thukral, to include cDNAs in the library which are

enriched for 5' cDNA from represented genes as taught by Guegler in order to improve the

construct of Fields in view of Thukral to achieve a hybrid gene library that could accurately test

whether different proteins (which would be full length proteins encoded by the cDNA library as

taught by Guegler as opposed to truncated proteins lacking N terminal sequences encoded by a

cDNA library made by more traditional methods, for example those that solely use a poly dT

primer) interact with a known protein in the method of Fields.

14.   Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fields in view of

Thukral, further in view of Guegler (Guegler et al; US Patent 6,083,727) as applied to claims 1-

4, 10-13, and 23-24 above, and further in view of Carson et al (US Patent, 5,679,647).

The teaching of Fields in view of Thukral and Guegler is set forth above.

Fields in view of Thukral and Guegler do not teach a hybrid gene cDNA library wherein

the regulatable DNA sequence is the rat Glucorticoid Response element. However, Carson

teaches an expression system that exploits glucocorticoid response elements responsive to a wide

variety of steroid hormones and teaches that pGREtk plasmid, which contains one or more rat

tyrosine amino transferase glucocorticoid response elements upstream of the thymidine kinase

promoter from pBLCAT8+, makes the pGREtk promoter particularly effective in stimulating

controlled overexpression of cloned genes in eukaryotic cells (see col. 14, lines 40-55). ·

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time

the invention was made to improve the regulatable DNA sequence in the vector used for making

hybrid gene cDNA libraries of Fields in view of Thukral and Guegler, by including rat

glucocorticoid response element for the purpose of making the regulatable DNA sequence in the

vectors of Fields in view of Thukral and Guegler more effective in stimulating the controlled

expression of cloned genes in eukaryotic cells. The ordinary artisan would have been motivated

to include rat glucocorticoid response element in the vector of Fields in view of Thukral and

Guegler because Carson teaches that using such response element is effective in stimulating the

controlled expression of cloned genes in eukaryotic cells.

15.   Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fields in view of

Thukral, further in view of Guegler (Guegler et al; US Patent 6,083,727) as applied to claims 1-

4, 10-13, and 23-24 above, and further in view of Le Douarin et al (Nucleic Acids Research, vol.,
23, pages 876-878, 1995).

The teaching of Fields in view of Thukral and Guegler is set forth above.

Fields in view of Thukral and Guegler do not teach a hybrid gene cDNA library wherein
the regulatable DNA sequence is an estrogen response element. However, Le Douarin teaches a
two hybrid assay which involves hybrid gene cDNA libraries wherein the vectors contain an
integrated URA3 reporter gene driven by one or three estrogen receptor response elements (see
page 876, col. 1, 2nd para). Le Douarin teaches that such system is particularly useful for large
screening of acidic activation domain tagged cDNA libraries. Therefore, it would have been
prima facie obvious to one of ordinary skill in the art at the time the invention was made to
improve the regulatable DNA sequence in the vector used for making hybrid gene cDNA
libraries of Fields in view of Thukral and Guegler, by including an estrogen response element
because Le Douarin teaches that such system is particularly useful for large screening of acidic
activation domain tagged cDNA libraries. The ordinary artisan would have been motivated to
improve the regulatable DNA sequence in the vector used for making hybrid gene cDNA
libraries of Fields in view of Thukral and Guegler, by including an estrogen response element
because Le Douarin teaches that such system is particularly useful for large screening of acidic
activation domain tagged cDNA libraries.

16.   Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fields in view of
Thukral, further in view of Guegler (Guegler et al; US Patent 6,083,727) as applied to claims 1-
4, 10-13, and 23-24 above, and further in view of Wagner et al (US patent 6,329,209).

The teaching of Fields in view of Thukral and Guegler is set forth above.

Fields in view of Thukral and Guegler do not teach a common peptide encoded by a molecule comprising sequence encoding all or part of the GAL4 yeast transcriptional activator and 6 successive histidine residues. However, Wagner teaches that proteins expressed by cDNA libraries can be purified wherein the proteins to be expressed which are encoded by the cDNA library are genetically fused to a histidine tag. Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the chimeric GAL4 activation domain protein of Fields in view of Thukral and Guegler to include a sequence within the vector that encoded both the GAL4 activation domain as well as 6 successive histidine tags because Wagner teaches that a histidine tag when genetically fused to an expressed peptide, allows the peptide expressed from a cDNA library to be purified. The ordinary artisan would have been motivated to modify the chimeric protein of Fields in view of Thukral and Guegler to include a histidine tag for the purpose of making the chimeric protein easier to purify.

17.   Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fields in view of Thukral, further in view of Guegler (Guegler et al; US Patent 6,083,727) as applied to claims 1-4, 10-13, and 23-24 above, and further in view of He et al (US Patent, 5,679,566).

The teaching of Fields in view of Thukral and Guegler is set forth above.

Fields in view of Thukral and Guegler do not teach a common peptide encoded by a molecule comprising sequence encoding all or part of the GAL4 yeast transcriptional activator and a nuclear localization sequence from SV40 virus. However, He teaches that GAL4-activation domain fusion proteins were targeted to the nucleus using the SV40 T antigen nuclear localization signal (NLS) (see col. 18, lines 10-45). He teaches that without the SV40 NLS, no B-galactosidase activity was detectable because nuclear localization had been eliminated.

Therefore, it would have been prima facie obvious to one ordinary skill in the art at the time the

invention was made to modify the chimeric GAL4 activation domain protein of Fields in view of

Thukral and Guegler to include a sequence within the vector that encoded both the GAL4

activation domain as well as SV40 NLS because He teaches that without the SV40 NLS, no B-

galactosidase activity was detectable because nuclear localization had been eliminated. The

ordinary artisan would have been motivated to modify the chimeric protein of Fields in view of

Thukral and Guegler to include the SV40 NLS because the assay taught by Fields uses B-

galactosidase activity as a measure of interaction between the interaction of GAL4 DNA binding

and GAL4 activation domain.

18.   Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thukral.

        Thukral teaches a method of constructing a cDNA library and inserting the library into a

signal trap vector to generate a signal trap library (hybrid gene library of instant claim 1, see col.

2, lines 40-50). The signal trap library (hybrid gene library) taught by Thukral is constructed

with vectors such that DNA sequences which control expression of section or marker genes,

cDNA inserts, and reporter genes are operably linked to said cDNA and genes and that the signal

sequences are inserted in frame to the reporter polypeptide coding sequences (see col. 7, lines 5-

15). Thukral teaches that the vector is pYYa-41L which is an E. coli –yeast shuttle vector that

contains a Bla1 gene for ampicillin resistance and TRP1 gene for propagation in yeast

('selectable marker sequence'). Thukral specifically teaches a vector which contains ColE1-ORI

replication origin for maintenance and propagation in E coli (instant claim 2), and a 2u origin for

replication and propagation in yeast (instant claims 3 and 10, see col. 7, lines 15-19). Thukral

also teaches that the vector contains in order 5' to 3' an ADH promoter (regulatable DNA

sequence), a polylinker containing unique XhI and Not I sites to facilitate directional cloning of

random primed cDNAs (multiple cloning site that does not encode a translational termination

sequence and placed immediately 3' to the regulatable DNA sequence, see also col. 10, lines 34-

37), a leaderless a-amylase gene encoding amino acids 29-624 of a-amylase (a DNA sequence

encoding at least one common peptide and not containing a translation initiation codon which is

place 3' to the multiple cloning site) (see col. 7, lines 20-26), or amino acids 82-624 (see col. 10,

lines 58-67). With regard to the limitation reciting "wherein the hybrid protein region lacks a

translation initiation codon 5' of the cDNA, although Thukral does not explicitly teach that the

vector lacks a translation initiation sequence other than that in a cDNA insert, Thukral does teach

at col 10, lines 34-40, how the vectors pYYA-41L and pYYA-2 were made. Thukral teaches

that in making the vectors from pGBT9, sequences between the ADH promoter and ADH

terminator were removed. Thus, the sequence directed to the GAL4 translation initiation

sequence was specifically taught by Thukral to have been removed. The vectors are then

described by what elements they do contain at col 7. Thukral teaches that the cDNA molecules

can be selected for the presence of 5' ends (see col. 4, lines 19-25; instant claimed limitation

"wherein the plurality of plasmid vectors contain a plurality of cDNA molecules generated using

random primers and enriched for 5' cDNA..."). With regard to the limitations reciting "at least

one GAL4 common peptide", such term is not specifically defined in the specification to be

limited to any particular portion of GAL 4. A "GAL4 common peptide" encompasses a

minimum of 2 consecutive amino acids from any portion of GAL4. The portion of a-amylase

taught by Thukral possesses at least 2 consecutive amino acids from any portion of GAL4. With

regard to the broad recitation "wherein at least one of the plurality of plasmid vectors is operable

in a GAL4 yeast two hybrid assay" the claimed vectors have not been specifically defined in the

specification to be limited to any type of activity or operability, nor does the claim limit the

vectors to any specific type of "operability". Thus the broad recitation imparts no structural

limitation on the claimed vectors other than, for example, that they be able to be cloned in a cell

also used for a yeast two hybrid assay, which does not distinguish the instant claims from the

disclosure of Thukral. Furthermore, it should be noted that the claims are directed to products,

not methods directed to a yeast two hybrid assay with specific steps. As such, the claimed

recitation is drawn to an intended use limitation that is not given patentable weight because it

provides no specific structural limitation to distinguish the claimed products from those disclosed

by Thukral.

With regard to claim 12, although Thukral does not specifically teach a vector that

contains selectable marker sequences such as the kanamycin for bacterial antibiotic resistance

and the yeast URA3 nutritional auxotrophy gene, Thukral does teach that vectors can be

constructed to contain selection genes such as URA (see col. 4 line 67) for growth in yeast and

kanamycin for antibiotic resistance in bacteria (see col. 5, lines 4-5). Therefore, it would have

been prima facie obvious to one of ordinary skill in the art at the time the invention was made to

construct a vector for hybrid gene libraries that contained as selection markers, the kanamycin

gene and the URA gene because Thukral teaches that vectors for use in making such libraries can

contain such selection genes. The ordinary artisan would have been motivated to construct a

vector for hybrid gene libraries that contained as selection markers, the kanamycin gene and the

URA gene because Thukral teaches to make vectors for use in making such libraries containing

such selection genes.

Conclusion

19.   Applicant's amendment necessitated the new ground(s) of rejection presented in this

Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE

MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this

final action.

20.   No claims are allowable over the cited prior art.

21.   Any inquiry concerning this communication or earlier communications from the

examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-

0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and

on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this

Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding

should be directed to (571) 272-0547.

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